

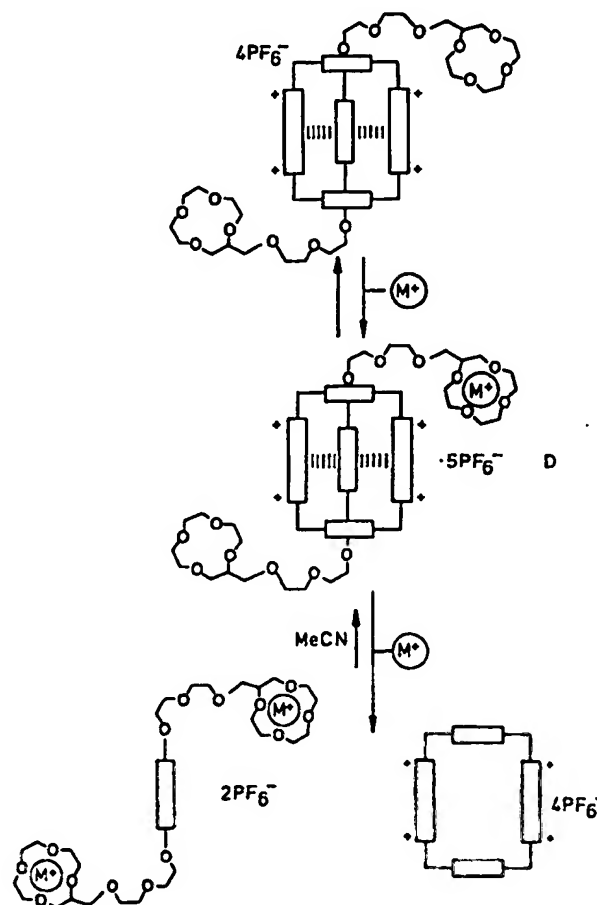
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(54) Title: **CHEMICAL COMPLEXES**

(57) Abstract

Rotaxanes and pseudorotaxanes, methods of making them, intermediates in their formation and methods of using them in sensors are provided based upon changes in colour absorption upon cation contact.



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Chemical Complexes

The present invention relates to chemical complexes in particular rotaxanes and pseudorotaxanes formed by addition of cationic cyclophanes and acyclic polyether derivatives, polyether derivatives useful in the preparation of such rotaxanes and pseudorotaxanes, uses of such rotaxanes and pseudorotaxanes and devices incorporating such rotaxanes and pseudorotaxanes.

There has been considerable recent interest concerning the control of molecular architectures in both the solid state and in solution. The known processes of molecular recognition and self-assembly have been employed to generate a number of topologically interesting and functioning supramolecular entities. One such known complex, a [2]pseudorotaxane (illustrated herein) is formed by interaction of two components, viz an acyclic polyether derivative containing a π -electron rich unit and an encircling π -electron deficient cyclophane unit.

The purpose of the present invention is to provide by interaction of a cyclophane and an acyclic polyether derivative a novel rotaxane or pseudorotaxane complex which has unexpected novel and useful properties. Where reference is made hereafter to rotaxanes, including the claims, it should be taken to include reference to pseudorotaxanes also.

According to the present invention in a first aspect there is provided a rotaxane complex which is formed by interaction between an acyclic polyether derivative containing one or more π -electron rich units and an encircling π -electron deficient cyclophane unit, the acyclic polyether chain having terminal units inhibiting slippage of the cyclophane from the thread, at least one of the terminal units comprising a cation receptor unit.

The rotaxane complex of the first aspect is therefore formed by π - π interaction between two compounds, Components 1 and 2, described as follows.

Component 1 is an acyclic polyether derivative containing one or more than one π electron rich functional units. Preferably component 1 has at least two different π electron rich functional units. The π electron rich units may or may not be aromatic. Examples include 1,4 dioxymethylene, 1,5

dioxynapthalene, tetrathiafulvalene groups.

The acyclic polyether thread of Component 1 may be of the same length or of different lengths at either side of the π electron rich units.

Component 1 may be of the structure provided in Figure 1 wherein R^1 and R^2 are neutral terminal units at least one of which includes a cation receptor site, eg a crown ether unit; n is zero or a positive integer, m is independently zero or a positive integer and p is independently zero or a positive integer; X and Y each represent a covalent bond or a π -electron-rich functional unit but where X may or may not be the same as Y , and at least one of X and Y is an π -electron-rich functional unit. Preferably x and y are different.

The thread has terminal units which may inhibit slippage of the cyclophane from the chain. Such terminal stopper units may allow or slightly inhibit dissociation of Components 1 and 2 where they are relatively small (pseudorotaxanes) or may prevent dissociation under most normal conditions where they are larger units (rotaxanes). At least one of the terminal units is preferably a neutral cation receptor unit. Examples of suitable neutral, cation-binding terminal units are macrocyclic polyethers such as crown-ethers, azacrown ethers, thiocrown ethers. Examples of non-cation binding terminal units are: SiR_3 , $SiPh_3$ (where R may be alkyl, arylalkyl etc; Ph is phenyl etc), OH , OR (R = alkyl), SH , NH_2 .

The terminal unit may be of crown form according to the formulae $a - crown - b$ where a is the number of atoms in the cyclic unit and b is the number of hetero atoms in the ring, with a varying between 8 and 45, preferably 8 and 24 and b varying between 3 and 25, preferably 3 and 10.

The crown ether may be specific for one or more types of or particular cations. For instance 12 - crown 4 is lithium ion specific.

Component 2 is a π electron deficient cyclophane. A cyclophane is a large ring compound incorporating aromatic units in the ring, one or more of the aromatic units being a π -electron deficient aromatic unit.

The cyclophane unit exists as a cationic compound and is associated with anion(s) to counterbalance the charge(s), for

instance in tetracationic form. A variety of anions (eg halides) may be employed in the cyclophane, although PF_6^- ions are preferred because of the enhanced solubilities they provide in organic solvents. Solubilities in different solvents can be controlled by careful choice of anions.

The said rotaxane is usually formed in a liquid medium, but may exist in either the solid state or in solution.

According to the present invention in a second aspect there is provided a cation complexed to a rotaxane as defined in the first aspect at the cation receptor site of at least one of its said terminal units.

According to the present invention in a third aspect there is provided a method of detecting a cation in a medium in contact with the rotaxane which comprises detecting changes in the intensity and/or wavelength of the absorption spectrum of the rotaxane.

In the method of the third aspect the rotaxane molecules are desirably aggregated and supported. For example; they may be deployed as a discrete region, eg formed by screen printing, in a thin film supported on a suitable substrate of glass or polymeric material. Alternatively, they may be formed as a film attached to, for instance, a polymer or siliceous surface. Furthermore, a thin film sensor element incorporating the rotaxane molecules may be incorporated into a photodetection system using either an optical waveguide and photodetector or photodetectors or low noise charge coupled devices (CCDs).

The method of detection according to the third aspect may comprise detecting a change in the absorption intensity at a given wavelength or a change in the ratio of absorption intensities at two different wavelengths. Detection of the said change may be carried out in one of the ways well known to those skilled in the photodetection art, eg by observing changes in the radiation reflected or transmitted after absorption using a spectrophotometer or a photodetector optionally with a colour filter.

The cation to be detected may comprise any metal ion, eg. Cs^+ or non-metal cation, eg an ammonium or alkylammonium ion or

zwitterionic species. The presence or a measure of the concentration of cations may be detected by measuring changes in the absorption spectrum of the rotaxane according to the first aspect.

The method according to the third aspect is useful in a variety of applications. Solutions containing cations to be detected by the method according to the third aspect may for example be produced in the following ways:

(i) the decontamination of surfaces contaminated with radioactive, toxic or other metal species, eg using as a decontamination agent an inorganic acid such as nitric, sulphuric or fluoroboric acid or an organic acid such as citric or formic acid;

(ii) as aqueous liquids produced in chemical streams;

(iii) as effluent streams produced by chemical processing operations;

(iv) as biological samples such as blood, serum etc.

In all of these applications samples may be produced which, with various known degrees of pre-treatment, may be converted into aqueous test samples for metal ion sensing or analysis by the method according to the fourth aspect.

The cation to be detected may comprise for example an alkali metal ion. The presence or concentration of radioactive caesium, for example, may advantageously be detected using the absorption spectrum of the rotaxane of the first aspect of the present invention in the method of the third aspect.

The method according to the third aspect of the present invention therefore provides a particularly convenient way of detecting cations present as trace components in a test solution.

According to the present invention in a fourth aspect there is provided an acyclic polyether derivative which comprises Component 1 as specified hereinbefore.

The polyether derivative of the fourth aspect may for example be prepared from an equivalent precursor molecule having terminal hydroxyl groups. This diol may be treated to afford its corresponding bistosylate eg. by use of tosyl chloride. The bistosylate may be reacted with the appropriate crown ether

molecules, eg. using sodium hydride in a suitable solvent such as tetrahydrofuran.

According to a fifth aspect of the invention we provide a device for detecting the presence of one or more cations in a medium, the device comprising a sensor provided with one or more rotaxanes or pseudorotaxanes according to the first aspect of the invention and means for monitoring the light absorption characteristics of the sensor.

The device may provide a qualitative or quantitative reading. The device may be specific to certain classes of cations, such as a particular group of the periodic table, or be specific to an individual cation for instance caesium.

Embodiments of the present invention will now be described by way of example with reference to the accompanying drawings, in which:

Figure 1 illustrates the structure of an acyclic polyether useful in the formation of rotaxanes and pseudorotaxanes;

Figure 2 illustrates a specific example of the structure of a compound having the structure shown in Figure 1;

Figure 3 illustrates a preparative route to a novel acyclic polyether useful in the formation of rotaxanes and pseudorotaxanes;

Figure 4 illustrates the structure of a known cyclophane.

Figure 5 illustrates formation of a rotaxane/pseudorotaxane embodying the present invention.

Figure 6 illustrates metal binding by a rotaxane/pseudorotaxane embodying the present invention.

Figure 1 illustrates a general formula of acyclic polyether compounds suitable for use in the present invention. In Figure 1, R^1 and R^2 are neutral terminal units at least one of which includes a cation receptor site, n , m and p are all zero or positive integers and may be the same or different, and x and y each represent a covalent bond or a π -electron-rich functional unit, but where x may or may not be the same as y (and preferably is not) and at least one of x and y is a π -electron-rich functional unit. Figure 1 also illustrates examples of x and y in a non-limiting sense.

A specific illustrative example of a compound of structure corresponding to component 1 is illustrated in Figure 2a. The structure is also shown in Figure 2b by a schematic representation.

The 1,4-bis(2-(2-(methoxy-12-crown-4)ethoxy)ethoxy)benzene illustrated in Figure 2 may be prepared as follows and as illustrated in Figure 3.

This compound may be prepared in two steps from its known corresponding diol, designated as structure F in Figure 3.

Tosylation of the diol using tosylchloride, triethylamine, 4-dimethylaminopyridine and dichloromethane affords the corresponding bistosylate, designated as structure G in Figure 3.

Reaction of two equivalents of 2-(hydroxymethyl)-12-crown-4, designated as molecule H in Figure 3, with the bistosylate in tetrahydrofuran (THF) and in the presence of sodium hydride yields the dumb-bell shaped molecule illustrated in Figure 2 in 70 per cent yield.

The following data was obtained to characterise the molecule referred to above:

FABMS 662(M⁺)

A specific illustrative example of Component 2 is the tetracationic cyclophane shown in Figure 4a. The structure is also shown in Figure 4b by a schematic representation.

Rotaxanes and pseudorotaxanes of the present invention are as noted above formed by interaction of Components 1 and 2 as specified above.

Rotaxanes may be made by one of two known assembly mechanisms, viz (i) a first mechanism in which the cyclophane is clipped around the π -electron rich molecule or (ii) a second mechanism in which an elevated temperature allows the cyclophane to slip over one of the end groups of the π -electron rich molecule. The terminal groups may in principle be added to Component 1 after the rotaxane has been formed but it is likely in practice that the ether chain will be derivatised with terminal groups before it is added to Component 2.

Figure 5 illustrates an example of formation of rotaxane from Components 1 and 2. Referring to Figure 5, the acyclic polyether derivative is converted into the multitopic [2]pseudorotaxane, designated in Figure 5 as molecule of structure C, using the cyclophane as follows. Equimolar solutions of the polyether molecule and the cyclophane both in acetonitrile, are added together at room temperature, 20°C. An intense red/orange colour appears instantaneously on addition of the two components. Combination of Components 1 and 2 in solution in this way leads to a π - π stacked complex by the mechanism of self-assembly in which the cyclophane encircles the acyclic polyether chain.

UV spectroscopic analysis of this solution reveals a charge-transfer between the π electron rich Component 1 and the π electron deficient cyclophane Component 2 which causes absorption of radiation at characteristic wavelengths. Desirably, this provides selective absorption of visible light characteristic of the rotaxane complex. In this example the rotaxane exhibits a strong red/orange colouration; an absorption band in the spectrum at $\lambda_{\text{max}} = 466 \text{ nm}$.

A ^1H NMR spectroscopic titration experiment (25°C, 300 MHz) yielded a binding constant K_a value of $610 \text{ dm}^3 \text{ mol}^{-1}$ for the complex. This binding constant is relatively large indicating that in acetonitrile solution a [2] pseudorotaxane is the predominant species. As will be noted from the structure shown in Figure 5 the aromatic unit of the polyether molecule forms a 1:1 inclusive bond in the interior of the cyclophane of structure.

The mode of action of the rotaxane molecule of Figure 5 on encountering a metal or other cation is illustrated in Figure 6. The addition of an excess metal cation, eg Na^+ , to a solution of the rotaxane leads to a binding of the cation (indicated in Figure 6 by symbol M^+) to a terminal crown ether group to form the unstable metal complex having a structure designated D in Figure 6. Electrostatic repulsion is produced in the complex between the two cation sites and this results in displacement of the cyclophane unit. Partial, or as illustrated in Figure 6,

total de-threading may occur, in either case the charge transfer is destroyed.

If the polyether chain contains only one electron rich/donor unit, charge transfer is no longer possible and the absorption band and resulting colour is diminished. If the polyether chain contains another second, but different, electron rich/donor unit, the cyclophane will be displaced onto this unit preferentially to the ether chain, allowing absorption at a different wavelength, resulting in a colour change. These effects provide the basis of a cation detector since detection of the change or reduction of the charge transfer absorption provides a measure of cation concentration.

In order to quantify the effect, the addition of molar proportions of either LiPF_6 or NaPF_6 to the [2]pseudorotaxane of structure Figure 5 in CD_3CN was carried out and led to a gradual suppression of the charge transfer absorption band in the spectrum of the complex of structure D. The addition of a large excess (>10 equivalents) of alkali metal cations brought about almost complete suppression of this absorption band, indicating that the tetracationic cyclophane component was no longer encircling the π -electron rich aromatic portion of component.

Further evidence of dethreading on metal addition was provided by analysis by Liquid Secondary Ion Mass Spectrometry (LSIMS) of the rotaxane complex of Figure 5. This revealed peaks at m/z 1617, 1472, 1372 corresponding to the loss of one, two and three counterions, respectively. However, the spectrum of the complex following the addition of a solution of LiPF_6 or NaPF_6 in CD_3CN revealed a dramatic decrease in the intensities of all of those previously observed peaks, indicating again that the [2]pseudorotaxane had dissociated upon addition of a source of metal cations.

As before mentioned where the polyether thread contains another, second, but different donor unit/ π -electron-rich unit, the cyclophane will preferentially reside on one of the aromatic donor sites yielding a rotaxane complex absorbing radiation at a characteristic wavelength. However, if a cation is introduced then the electro-static repulsion between the bound cation and

the cyclophane unit of the rotaxane causes the cyclophane to dissociate from that π -electron-rich unit. As a result the preferential cyclophane to π -electron-rich unit association is disrupted and the cyclophane instead associates with the alternative π -electron-rich unit. This gives rise to the pseudo-rotaxane complex absorbing radiation at a different characteristic wavelength.

The aforementioned concept has been demonstrated using a polyether thread containing both 1,4 - dioxypyrene and 1,5 - dioxynaphthalene donor groups. This polyether thread was synthesised from known precursors in a five step synthesis.

1,4-bis [2- (2-hydroxyethoxy) ethoxy] benzene, F in Figure 3, was mono-protected using triisopropyl chloride, imidazole and 4-dimethylaminopyridine in dichloromethane. Tosylation of this compound with toluene-p-sulfonyl chloride, 4-dimethylaminopyridine and triethylamine in dichloromethane afforded 1- [2- (2-toluene-p-sulfonyloxy) ethoxy] -4- [2- (2-(triisopropylsiloxy) ethoxy) ethoxy] - benzene.

1,5-bis [2- (2-hydroxyethoxy) ethoxy] naphthalene was mono-protected using dihydropyran in dichloromethane in the presence of a catalytic amount of pyridinium toluene-p-sulfonate.

Alkylation of this naphthalene derivative with the aforementioned monotosylate using sodium hydride in tetrahydrofuran yielded an unsymmetrical, two donor thread which was subsequently mono-deprotected using pyridinium toluene-p-sulfonate in ethanol to give the required compound.

Addition of cyclophane to an acetonitrile solution of the compound yielded a purple complex which absorbs radiation at 518nm. This indicates the formation of a pseudorotaxane structure in which the cyclophane resides preferentially on the 1,5-dioxynaphthalene donor group.

Characterisation of the unsymmetrical thread -

^1H (CDCl₃, 300 MHz) δ 1.06 (21 H, brs, Si(C(CH₃)₂)₃), 3.65-3.86 (20 H, m, OCH₂), 3.98-4.03 (8 H, m, OCH₂), 4.28-4.30 (4 H, m, OCH₂), 6.81 (4 H, s, HQ), 6.83 (2 H, d, J - 8Hz, NPH2H6), 7.35 (2 H, t, J - 8 Hz, NPH3H7), 7.86 (2 H, m, NPH4H8)

^{13}C (CDC13, 75 MHz) δ 12.0, 18.0, 61.9, 63.1, 67.9, 68.2, 69.8, 70.0, 70.8, 71.0, 72.6, 72.9, 105.8, 114.5, 114.8, 115.5, 125.0, 125.3, 126.8, 153.1, 154.3.

MS (FAB) M^+ 760

As a consequence when the cyclophane unit interacts with a 1,4-dioxybenzene unit the characteristic absorption is $\lambda = 466$ nm. When the cyclophane unit interacts with the 1,5-dioxynaphthalene unit the characteristic absorption is $\lambda = 518$ nm. Movement of the cyclophane unit from one unit to another due to repulsion by a cation bound to one of the terminal units affords a measurable change in absorption intensity at the given wavelength - this can be correlated to cation concentration.

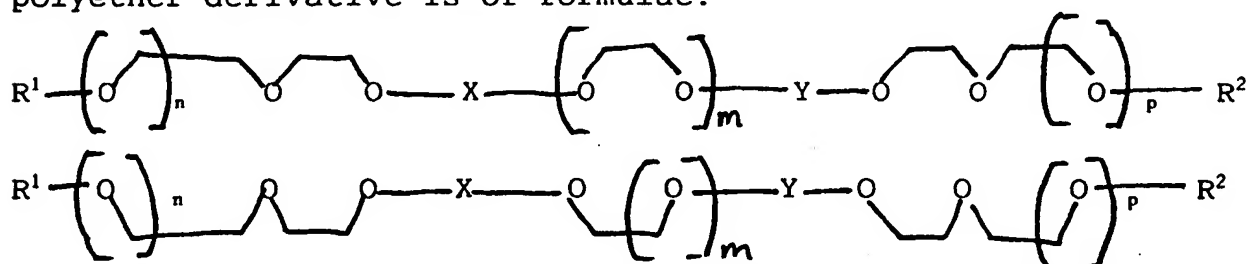
With just one π -electron-rich area complete colour loss for a given molecule can give a similarity correlated effect.

As a consequence the detector employing both π -electron-rich groups provides means by which cations concentration can be determined.

Claims

1. A rotaxane or pseudorotaxane complex which is formed by interaction between an acyclic polyether derivative containing one or more π -electron rich units and an encircling π -electron deficient cyclophane unit, characterised in that the acyclic polyether chain has terminal units inhibiting slippage of the cyclophane from the chain, at least one of the terminal units comprising at least one cation receptor-unit.

2. A rotaxane complex according to Claim 1 in which the polyether derivative is of formulae:-



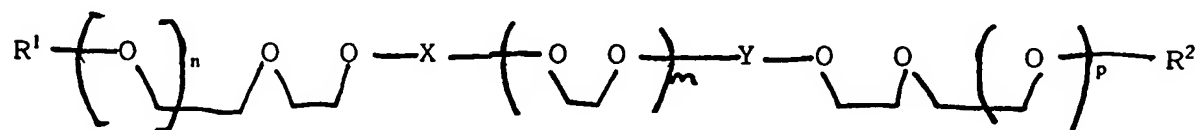
in which R^1 and R^2 are neutral terminal units at least one of which includes a cation receptor site; n , m and p are independently either zero or a positive integer; x and y each represent a covalent bond or a π -electron-rich functional unit, where x is not the same as y and at least one of x and y is a π -electron-rich functional unit.

3. A rotaxane complex as in Claim 1 or Claim 2 and wherein the polyether derivative includes one or more π -electron rich aromatic units.

4. A rotaxane complex as in Claim 3 and wherein the polyether derivative includes one or more π -electron rich 1,4 dioxylene, 1,5 dioxynaphthalene or tetrathiofulvalene groups.

5. A rotaxane complex as in any one of Claims 1 to 4 and wherein at least one of the terminal units is selected from crown ethers, azacrown ethers, and thiocrown ethers, cyclams, porphyrins, calixanes, calixacrowns and calixaspherands.

6. A rotaxane complex as in any one of the preceding claims and wherein the cyclophane unit comprises an ionic compound.
7. A rotaxane complex as in Claim 6 and wherein the cyclophane is charge balanced by one or more PF_6^- anions.
8. A rotaxane as in any one of the preceding claims and which has a cation complexed thereto at the cation receptor site of at least one of its said terminal units.
9. A method of detecting the presence or concentration of cations in a medium which includes bringing a rotaxane as in any one of Claims 1 to 6 into contact with the medium and detecting changes which occur in the absorption spectrum of the rotaxane.
10. A method as in Claim 9 and wherein the rotaxane comprises molecules which are aggregated and supported on a substrate.
11. A method as in Claim 9 or Claim 10 and wherein the rotaxane is specific to the cations to be detected.
12. An acyclic polyether derivative useful in the formation of a rotaxane as in any one of Claims 1 to 6 and wherein the polyether derivative is a compound having the formula:-

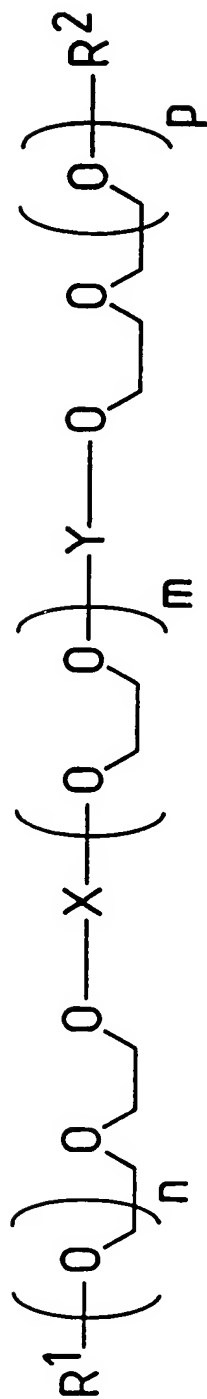


in which R^1 and R^2 are neutral terminal units at least one of which includes a cation receptor site; n , m and p are independently either zero or a positive integer; x and y each represent a covalent bond or a π -electron-rich functional unit, where x is not the same as y and at least one of x and y is a π -electron-rich functional unit.

13. An acyclic polyether derivative as in Claim 11 and wherein the polyether derivative is 1,4 - bis (2- (2- (methoxy-12-crown-

4) ethoxy) ethoxy) benzene or 1,5 - bis (2- (2-hydroxyethoxy) ethoxy) naphthalene or incorporates 1,4 - dioxybenzene and/or 1,5 - dioxynaphthalene.

14. A device for measuring or detecting the presence of a cationic species in a medium comprising a sensor provided with a rotaxane according to any of claims 1 to 9, and means to monitor the light absorbtion characteristics of the rotaxane.



Examples of
X or Y =

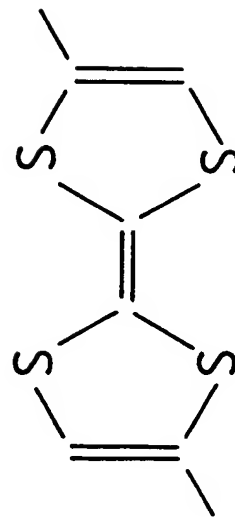
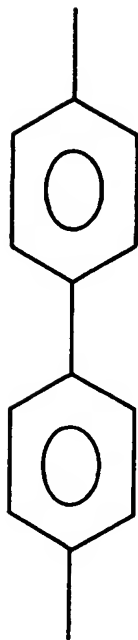
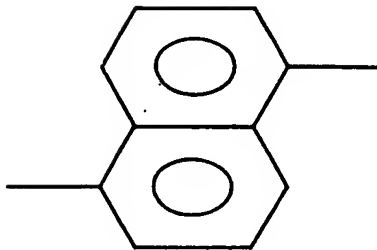


FIG. 1

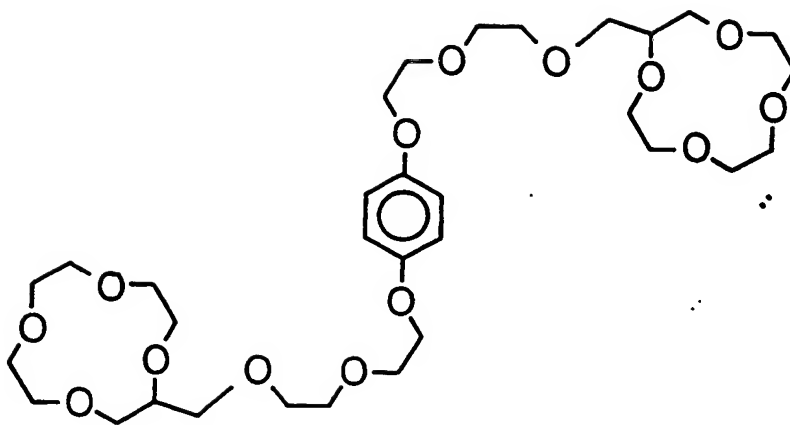


FIG. 2a

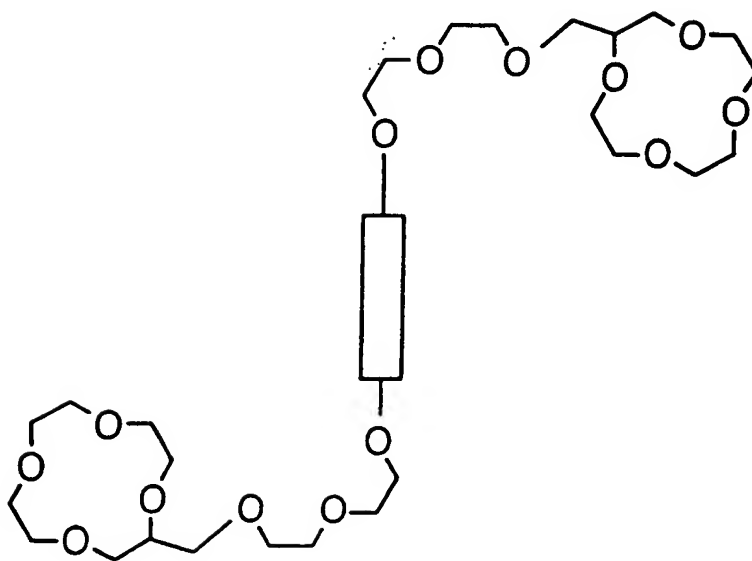


FIG. 2b

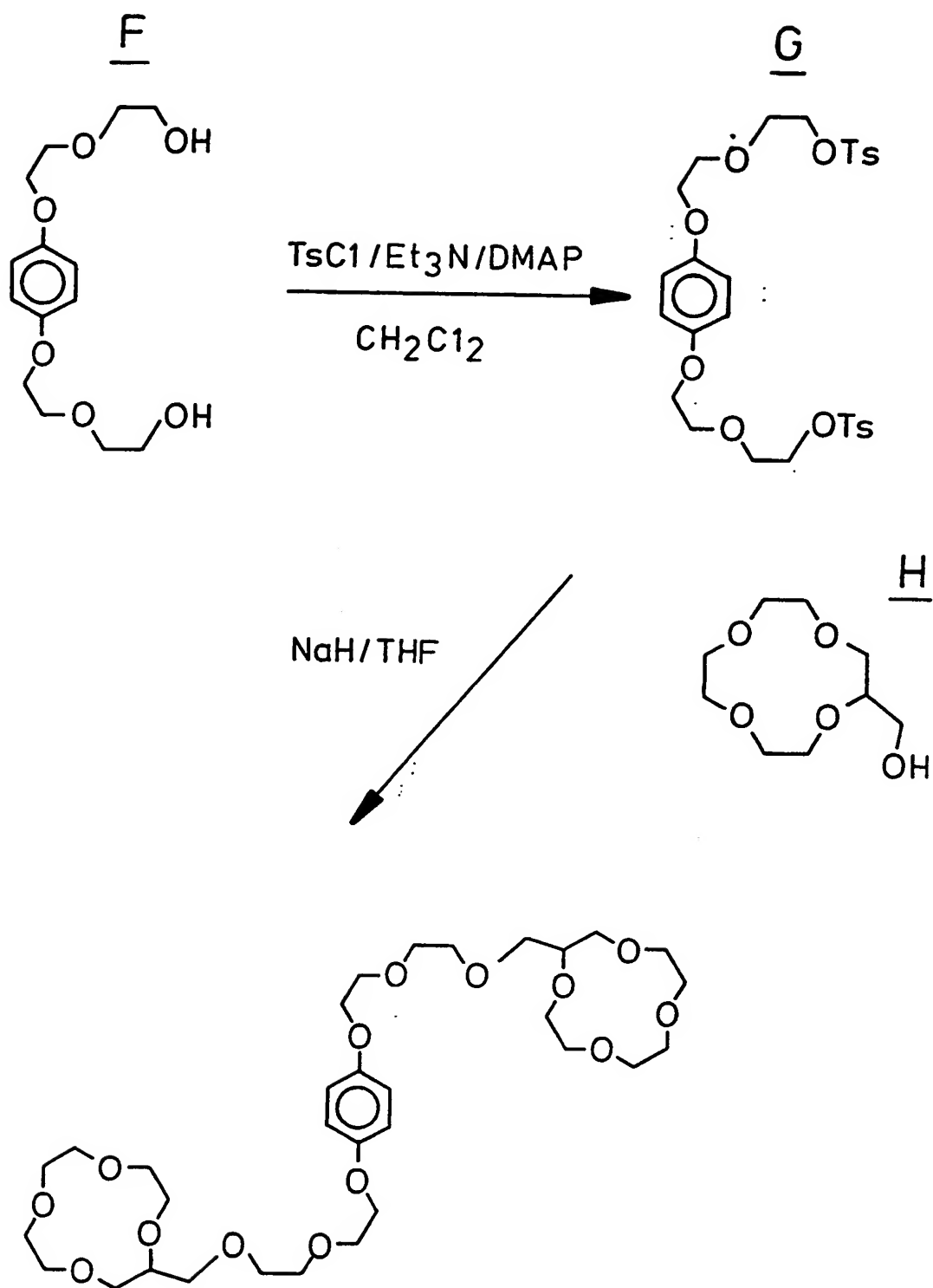


FIG. 3

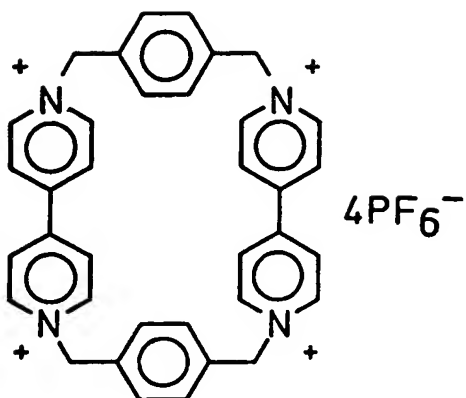


FIG. 4a

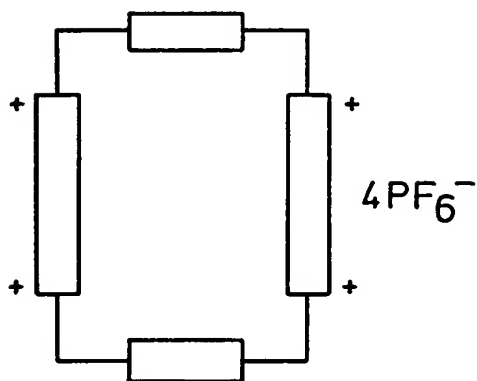
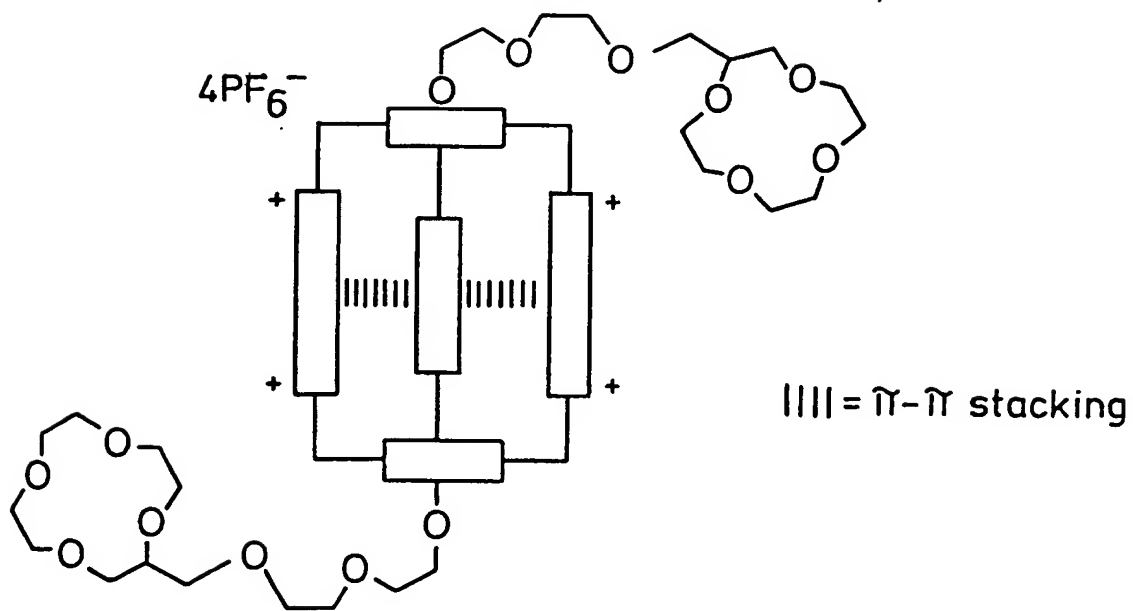
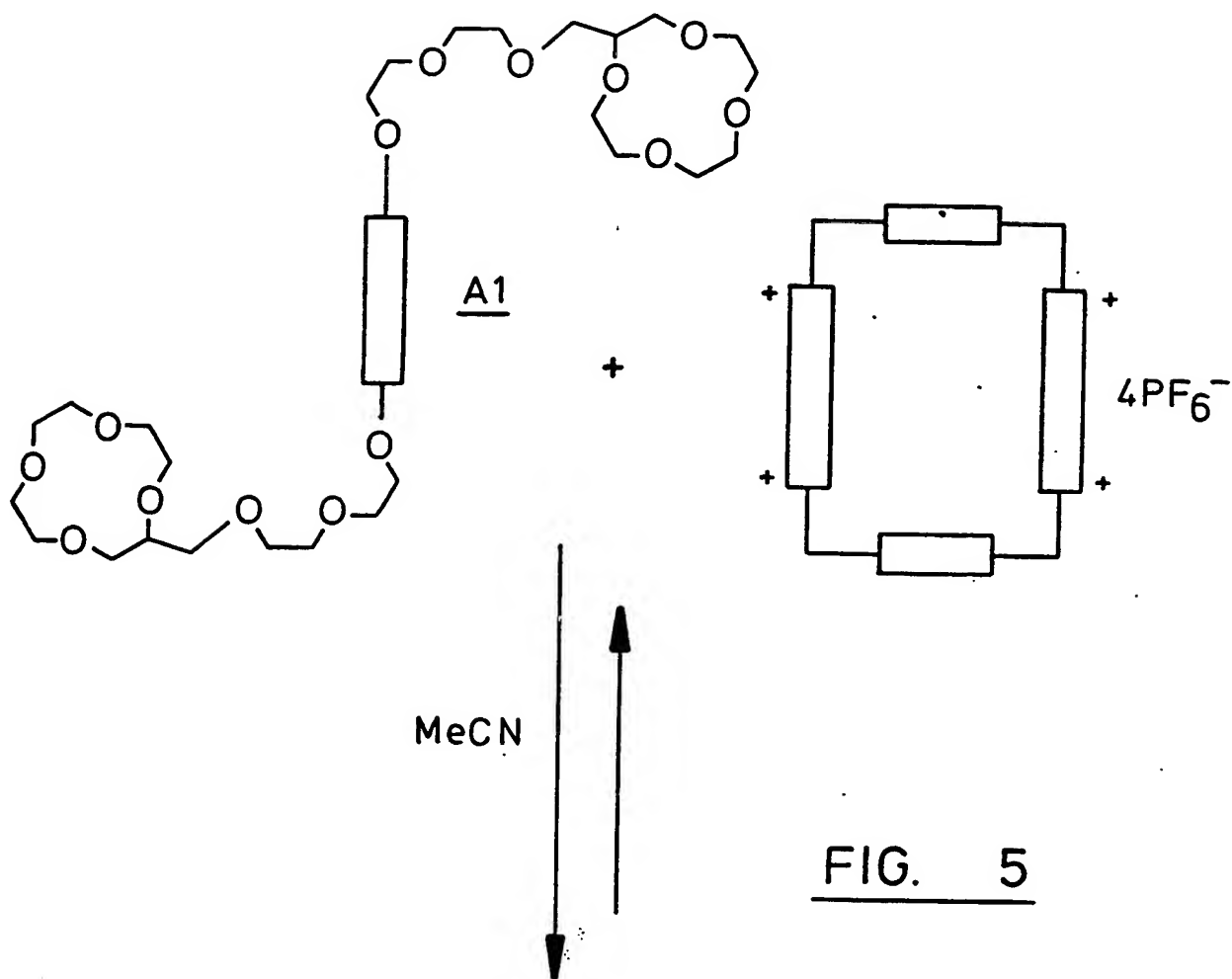
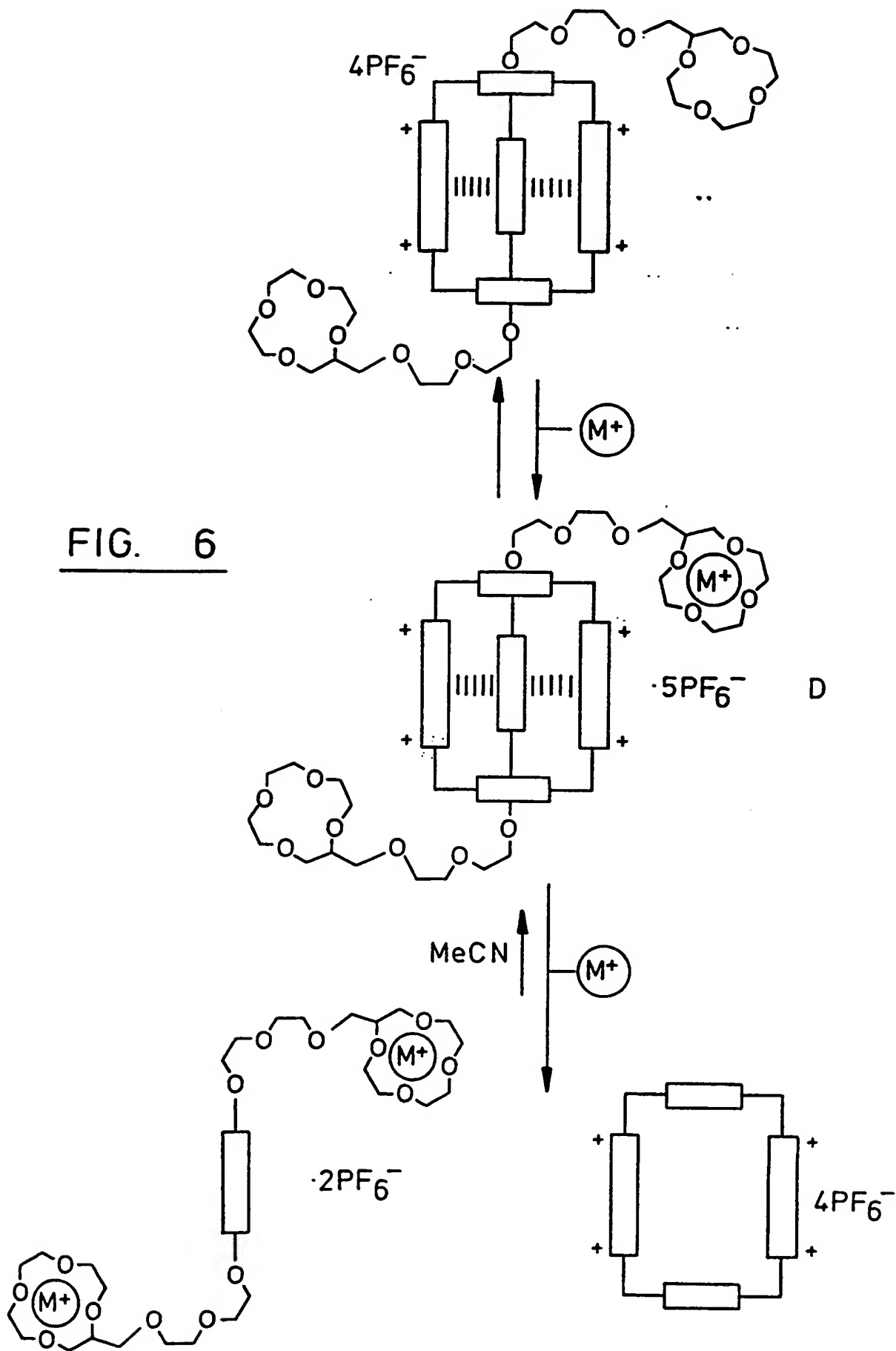


FIG. 4b





A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D323/00 C07D409/14 C08L71/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
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| A | EP,A,0 097 960 (SHIMADZU CORPORATION) 11 January 1984 see the whole document | 1,14 |
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Date of the actual completion of the international search

11 October 1996

Date of mailing of the international search report

25. 10. 96

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

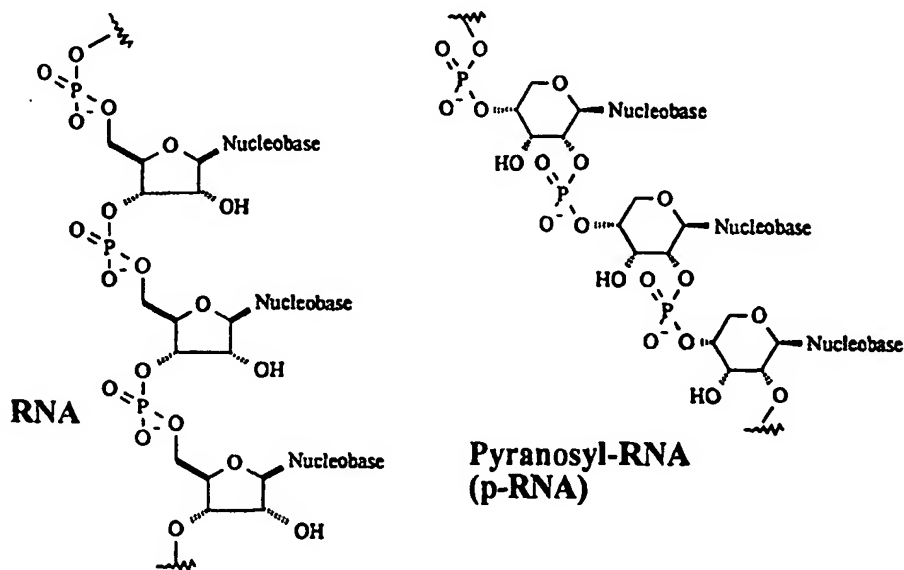
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|---|--|---|---|--|
| <p>(51) Internationale Patentklassifikation ⁶ : C07H 21/00, 19/04</p> | A3 | <p>(11) Internationale Veröffentlichungsnummer: WO 99/52923</p> <p>(43) Internationales Veröffentlichungsdatum: 21. Oktober 1999 (21.10.99)</p> | | |
| <table style="width: 100%;"> <tr> <td style="width: 50%; vertical-align: top;"> <p>(21) Internationales Aktenzeichen: PCT/EP99/02356</p> <p>(22) Internationales Anmeldedatum: 7. April 1999 (07.04.99)</p> <p>(30) Prioritätsdaten: 198 15 901.3 8. April 1998 (08.04.98) DE</p> <p>(71) Anmelder (für alle Bestimmungsstaaten ausser US): AVENTIS RESEARCH & TECHNOLOGIES GMBH & CO. KG [DE/DE]; D-65926 Frankfurt am Main (DE).</p> <p>(72) Erfinder; und (75) Erfinder/Anmelder (nur für US): ESCHENMOSER, Albert [CH/CH]; Bergstrasse 9, CH-8700 Küsnacht (CH). PITSCH, Stefan [CH/CH]; Regensdorferstrasse 45, CH-8049 Zürich (CH). WENDEBORN, Sebastian [CH/CH]; Kapellenweg 11, CH-4102 Binningen (CH).</p> <p>(74) Anwalt: BÖSL, Raphael; Bardehle, Pagenberg, Dost, Altenburg, Geissler, Isenbruck, Galileiplatz 1, D-81679 München (DE).</p> </td> <td style="width: 50%; vertical-align: top;"> <p>(81) Bestimmungsstaaten: AU, BR, CA, JP, KR, US, europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Veröffentlicht <i>Mit internationalem Recherchenbericht. Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.</i></p> <p>(88) Veröffentlichungsdatum des internationalen Recherchenberichts: 13. Januar 2000 (13.01.00)</p> </td> </tr> </table> | | | <p>(21) Internationales Aktenzeichen: PCT/EP99/02356</p> <p>(22) Internationales Anmeldedatum: 7. April 1999 (07.04.99)</p> <p>(30) Prioritätsdaten: 198 15 901.3 8. April 1998 (08.04.98) DE</p> <p>(71) Anmelder (für alle Bestimmungsstaaten ausser US): AVENTIS RESEARCH & TECHNOLOGIES GMBH & CO. KG [DE/DE]; D-65926 Frankfurt am Main (DE).</p> <p>(72) Erfinder; und (75) Erfinder/Anmelder (nur für US): ESCHENMOSER, Albert [CH/CH]; Bergstrasse 9, CH-8700 Küsnacht (CH). PITSCH, Stefan [CH/CH]; Regensdorferstrasse 45, CH-8049 Zürich (CH). WENDEBORN, Sebastian [CH/CH]; Kapellenweg 11, CH-4102 Binningen (CH).</p> <p>(74) Anwalt: BÖSL, Raphael; Bardehle, Pagenberg, Dost, Altenburg, Geissler, Isenbruck, Galileiplatz 1, D-81679 München (DE).</p> | <p>(81) Bestimmungsstaaten: AU, BR, CA, JP, KR, US, europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Veröffentlicht <i>Mit internationalem Recherchenbericht. Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.</i></p> <p>(88) Veröffentlichungsdatum des internationalen Recherchenberichts: 13. Januar 2000 (13.01.00)</p> |
| <p>(21) Internationales Aktenzeichen: PCT/EP99/02356</p> <p>(22) Internationales Anmeldedatum: 7. April 1999 (07.04.99)</p> <p>(30) Prioritätsdaten: 198 15 901.3 8. April 1998 (08.04.98) DE</p> <p>(71) Anmelder (für alle Bestimmungsstaaten ausser US): AVENTIS RESEARCH & TECHNOLOGIES GMBH & CO. KG [DE/DE]; D-65926 Frankfurt am Main (DE).</p> <p>(72) Erfinder; und (75) Erfinder/Anmelder (nur für US): ESCHENMOSER, Albert [CH/CH]; Bergstrasse 9, CH-8700 Küsnacht (CH). PITSCH, Stefan [CH/CH]; Regensdorferstrasse 45, CH-8049 Zürich (CH). WENDEBORN, Sebastian [CH/CH]; Kapellenweg 11, CH-4102 Binningen (CH).</p> <p>(74) Anwalt: BÖSL, Raphael; Bardehle, Pagenberg, Dost, Altenburg, Geissler, Isenbruck, Galileiplatz 1, D-81679 München (DE).</p> | <p>(81) Bestimmungsstaaten: AU, BR, CA, JP, KR, US, europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Veröffentlicht <i>Mit internationalem Recherchenbericht. Vor Ablauf der für Änderungen der Ansprüche zugelassenen Frist. Veröffentlichung wird wiederholt falls Änderungen eintreffen.</i></p> <p>(88) Veröffentlichungsdatum des internationalen Recherchenberichts: 13. Januar 2000 (13.01.00)</p> | | | |

(54) Title: **METHOD FOR THE PRODUCTION OF PENTOPYRANOSYL NUCLEOSIDES**

(54) Bezeichnung: **VERFAHREN ZUR HERSTELLUNG VON PENTOPYRANOSYL-NUCLEOSIDEN**



(57) Abstract

The invention relates to a method for the production of a pentopyranosyl nucleoside 3', 4'-cyclic acetal, whereby a pentopyranosyl nucleoside is made to react with an aldehyde, ketone, acetal or ketal under a vacuum.

(57) Zusammenfassung

Die Erfindung betrifft ein Verfahren zur Herstellung eines 3', 4'-cyclischen Acetals eines Pentopyranosyl-Nucleosids, bei dem ein Pentopyranosyl-Nucleosid mit einem Aldehyd, Keton, Acetal oder Ketal unter Unterdruck umgesetzt wird.

LEDIGLICH ZUR INFORMATION

Codes zur Identifizierung von PCT-Vertragsstaaten auf den Kopfbögen der Schriften, die internationale Anmeldungen gemäss dem PCT veröffentlichen.

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A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C07H21/00 C07H19/04

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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07H

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

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| A | <p>ESCHENMOSER ET AL: "147. Why pentose- and not hexose-nucleic acids?" HELVETICA CHIMICA ACTA, vol. 76, 1 January 1993 (1993-01-01), pages 2161-2183, XP002094190 ISSN: 0018-019X cited in the application page 2168 -page 2169</p> <p style="text-align: center;">--- -/--</p> | 1, 22, 24 |

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Date of the actual completion of the international search

10 November 1999

Date of mailing of the international search report

18/11/1999

Name and mailing address of the ISA

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| A | <p>M BHRINGER ET AL: "110. Warum Pentose- und nicht Hexose-Nucleins uren ? Oligonucleotide aus 2',3'-Dideoxy-B-D-glucopyranosyl-Bausteine n ('Homo-DNS?): Herstellung" HELVETICA CHIMICA ACTA, vol. 75, no. 5, 1 January 1992 (1992-01-01), pages 1416-1477, XP002096856 ISSN: 0018-019X cited in the application page 1421 page 1427 -page 1429</p> | 1,22,24 |
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| P,X | <p>WO 99 15540 A (BURDINSKI GERHARD ;MICULKA CHRISTIAN (DE); HOECHST AG (DE); WINDHA) 1 April 1999 (1999-04-01) claims 1-25; figures 2A,2B</p> | 1-31 |

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C. ALS WESENTLICH ANGESEHENE UNTERLAGEN

| Kategorie* | Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile | Betr. Anspruch Nr. |
|------------|--|--------------------|
| A | <p>ESCHENMOSER ET AL: "147. Why pentose- and not hexose-nucleic acids?" HELVETICA CHIMICA ACTA, Bd. 76, 1. Januar 1993 (1993-01-01), Seiten 2161-2183, XP002094190 ISSN: 0018-019X in der Anmeldung erwähnt Seite 2168 -Seite 2169</p> <p style="text-align: center;">--- -/--</p> | 1,22,24 |



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C (Fortsetzung) ALS WESENTLICH ANGEKÜNDIGTE UNTERLAGEN

| Kategorie | Bezeichnung der Veröffentlichung, soweit erforderlich unter Angabe der in Betracht kommenden Teile | Betr. Anspruch Nr. |
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| A | <p>M BHRINGER ET AL: "110. Warum Pentose- und nicht Hexose-Nucleins üren ? Oligonucleotide aus 2',3'-Dideoxy-B-D-glucopyranosyl-Bausteine n ('Homo-DNS?): Herstellung" HELVETICA CHIMICA ACTA, Bd. 75, Nr. 5, 1. Januar 1992 (1992-01-01), Seiten 1416-1477, XP002096856 ISSN: 0018-019X in der Anmeldung erwähnt Seite 1421 Seite 1427 -Seite 1429 ---</p> | 1,22,24 |
| A | <p>H.VORBRÜGGEN ET ALL.: "Nucleoside Synthesis with Trimethylsilyl Triflate and Perchlorate as Catalysts." CHEMISCHE BERICHTE, Bd. 114, 1981, Seiten 1234-1255, XP002121064 in der Anmeldung erwähnt das ganze Dokument ---</p> | 1,22,24 |
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| Im Recherchenbericht angeführtes Patentdokument | Datum der Veröffentlichung | Mitglied(er) der Patentfamilie | Datum der Veröffentlichung |
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